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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,036	02/09/2005	Maharaj K. Sahib	WH-2	1841

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EXAMINER

WOODWARD, CHERIE MICHELLE

ART UNIT	PAPER NUMBER
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1647

MAIL DATE	DELIVERY MODE
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01/21/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/524,036

Applicant(s)

SAHIB ET AL.

Examiner

CHERIE M. WOODWARD

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 12-22 and 29-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 23-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S508)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(c), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(c) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/20/2008 has been entered.

Formal Matters

2. Claims 1-36 are pending. Claims 12-22 and 29-36 remain withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonselected invention, there being no allowable generic or linking claim. Claims 1-11 and 23-28 are under examination.

Response to Arguments

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

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Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-11 and 23-28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al., US Patent 4,916,212 (10 April 1990) and Schweden et al., US Patent 5,672,487 (30 September 1997), as evidenced by Hollenberg et al., (Curr Opin Biotechnol. 1997 Oct;8(5):554-60, Abstract Only), Weidemann et al., (FEBS Lett. 1989. Oct 23; 257(1):31-4), and Weydemann et al., (Appl Microbiol Biotechnol. 1995;44:377-385), for the reasons of record and the reasons set forth herein.

Applicant notes that the prior Office Action contained a typographical error directed to the Markussen et al., patent (Remarks, p. 12, last paragraph to p. 13, first paragraph). The examiner thanks Applicant for bringing this to her attention. The correct US Patent number for the Markussen patent is 4,916,212 (as cited on the Notice of References Cited, mailed 10/5/2007).

Applicant argues that Markussen does not teach a DNA construct with the signal peptide sequence from *Schwanniomyces occidentalis* or *Carcinus maenas* crustacean hyperglycemic hormone (Remarks, p. 13, third paragraph). Applicant points out that the only disclosure of a glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is in a citation for a reference in the background section where the glucoamylase leader sequence was not part of the DNA constructs taught by Schweden (Remarks, p. 13, last paragraph). Applicant argues that Schweden teaches that Schweden teaches away from the instant invention at column 1, lines 28-36 because the GAM1 signal sequence is taught as not leading to the secretion of gene products foreign to yeasts and that Schweden was not able to secrete the protein hirudin using the GAM1 signal sequence (Remarks, p. 14, first two paragraphs).

Applicant argues that the examiner has engaged in hindsight reasoning (Remarks, p. 14, third paragraph). Applicant argues that the examiner's statements that the use of these signal sequences is proven, successful, and predictable, is not supported by Schweden (Remarks, p. 15, first paragraph). Applicant argues that the asserted prior art provides no working examples of the invention claimed in the instant application (Remarks, p. 15, first paragraph). Applicant argues that Schweden does not teach the yield of hirudin obtained using the process taught in the examples therein (Remarks, p. 15, second paragraph). Applicant argues that the only leader sequence used in Schweden is from shore crab (SEQ ID NO: 1) and that there is no disclosure or enablement for the use of the leader sequence from *Schwanniomyces occidentalis* (Remarks, p. 15, last paragraph to p. 16, first paragraph). Applicant also

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argues that there is no disclosure of insulin in Schweden and that no protein other than hirudin is specifically disclosed in Schweden (Remarks, p. 16, first paragraph).

Applicant argues that the instantly claimed process which is useful for making insulin "may not be useful for manufacturing other recombinant protein even when they belong to the same class" (Remarks, p. 16, first paragraph). Applicant admits that one of skill in the art could envision the use of the process involving the leader sequence obtained from the shore crab as claimed in Schweden for the production of hirudin and analogs, but that the production of insulin would not be envisioned (Remarks, p. 17, second paragraph). Applicant argues that the use of such a process for the production of insulin would require undue experimentation (Remarks, p. 17, second paragraph). Applicant argues that there is no teaching or suggestion that the MF-alpha leader sequence taught by Markussen in the production of pre-pro-insulin be substituted with the leader sequence of the shore crab taught by Schweden (Remarks, p. 17, last paragraph).

Applicant also argues that the instant invention has yielded unexpected results in that the use of the signal peptide sequences from either *Schwanniomyces occidentalis* or *Carcinus maenas* results in an unexpected high yield of insulin precursor (Remarks, p. 18, second paragraph). Applicant also argues that Schweden does not provide a level of predictability (Remarks, p. 18, third paragraph). In support of this argument, Applicant states that the use of signal sequences from *Schwanniomyces occidentalis* or *Carcinus maenas* were known only for the production of proteins which were present in yeast (Remarks, p. 18, sixth paragraph). Applicant argues that Schweden makes unsupported conclusory statements that the process leads to a high yield of mature proteins (Remarks, p. 18, sixth paragraph). Applicant argues that unexpected results must be established by factual evidence and that arguments or conclusory statements do not suffice (citing *In re De Blauwe*, 736 F2d 699, 705 (Fed. Cir. 1984)) (Remarks, p. 18, last paragraph to p. 19, first paragraph).

Applicant admits that at the time of the instant invention that recombinant insulin was a well-established product in the market and that there were a number of patents specifically disclosing the process of producing insulin using recombinant technology (Remarks, p. 19, second paragraph). Applicant argues that one of ordinary skill in the art would not predict the high yield of insulin by merely using the claimed signal sequences and process as taught by Schweden (Remarks, p. 19, second paragraph).

Applicant argues that Hollenberg's general disclosure does not describe or suggest the using a DNA construct comprising the signal sequences from *Schwanniomyces occidentalis* or *Carcinus maenas*,

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or alternatively, if Hollenberg does suggest the use of the DNA construct for the production of insulin, Hollenberg does not enable such a process (Remarks, p. 20, first paragraph).

Applicant argues that Weidemann does not disclose the cDNA sequence for the production of the insulin precursor nor does it disclose the cDNA sequence “which is not flanked by a cleavage site” (Remarks, p. 20, second paragraph). Applicant states that it would not be obvious to one of ordinary skill in the art to combine the references (Remarks, p. 20, third paragraph).

Applicant argues that the prior art does not suggest the desirability of the claimed modifications over the prior art (Remarks, p. 21, first paragraph). Applicant argues that the examiner engages in improper hindsight reasoning (Remarks, p. 21, second paragraph).

Applicant argues that the prior art references of record do not suggest any motivation, suggestion, or teaching to produce the instant invention, as claimed (Remarks, p. 21, second paragraph). Applicant cites *KSR International Co. v. Teleflex, Inc.*, 550 US ____ (2007) and *In re Wada et al.*, (BPAI 2008) in support of this argument (Remarks, p. 21, last paragraph).

Applicant argues that the Office Action fails to specifically address the expressly recited features of the claims, contrary to MPEP 707.07(g) and that this failure constitutes a “failure to expeditiously provide the information necessary to resolve issues related to the patentability that prevents the Applicant from, for example presenting appropriate patentability arguments and/or rebuttal evidence (Remarks, p. 22, first paragraph).

Applicant cites a number of cases, including *In re Mills* and *In re Sernaker* (Remarks, p. 22, last two paragraphs), *Orthopedic Equipment Co. v. United States, Uniroyal, Inc.*, v. *Rudkin-Wiley Corp.*, and *Ex parte Levengood* (Remarks, p. 23), *Ex parte Clapp* and *Ex parte Levengood* (Remarks, p. 24) to support arguments that: the prior art must suggest a desirability to combine the references; that the prior art must themselves teach or suggest the motivation to combine; that the suggestion to combine should not come from the Applicant; that a *prima facie* case must be established in the form of some teaching, suggestion, incentive, or inference in the applied prior art or in the form of generally available knowledge that one of ordinary skill in the art would have been led to combine the teachings of the prior art; and that the examiner include an explanation in the form of a factual basis to support the conclusion that it would have been obvious to make the combination.

Applicant’s arguments have been fully considered, but they are not persuasive. As set forth in the record, the claimed construct of the instant invention is a composition comprising a yeast promoter followed by a signal peptide from the recited species of *Schwanniomyces occidentalis* glucoamylase

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signal peptide sequence or *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequence, which is then followed by an insulin pre-pro-peptide (claim 1).

Regarding Applicant's argument that Markussen does not teach a DNA construct with the signal peptide sequence from *Schwanniomyces occidentalis* or *Carcinus maenas* crustacean hyperglycemic hormone (Remarks, p. 13, third paragraph), the examiner reiterates statements previously made of record, that Markussen teaches DNA constructs comprising human insulin precursors expressed in yeasts, thus meeting the some of the limitations of instant claims 1, 4-11, 23, and 25. The examiner also stated of record that Markussen does not teach a yeast DNA construct with signal sequences from the species of *Schwanniomyces occidentalis* glucoamylase or the *Carcinus maenas* crustacean hyperglycemic hormone. The '487 patent was cited as a combinatorial reference because it teaches construction of vectors for the secretory expression of recombinant proteins from the yeast *Hansenula polymorpha* including yeasts with the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* and the leader sequence from the hyperglycemic hormone of the shore crab (*Carcinus maenas*).

Regarding Applicant's argument that the only disclosure of a glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is in a citation for a reference in the background section where the glucoamylase leader sequence was not part of the DNA constructs taught by Schweden (Remarks, p. 13, last paragraph), Applicant misunderstands the point of the disclosure by Schweden. Schweden specifically states that "[t]he genuine signal sequences of a heterologous protein are also recognized in yeasts. In the yeast *Hansenula polymorpha*, the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is recognized as [a] signal sequence, and it is possible to secrete correctly processed glucoamylase [internal citation omitted]. However, this signal sequence does not lead to the secretion of gene products foreign to yeasts, for example it is not possible to secrete the protein hirudin therewith" (column 1, lines 26-35). It is not relevant that the teaching of Schweden is in the background section of the patent. The point of the teaching by Schweden is that the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is known in the art to be used in the secretion of heterologous non-yeast proteins in the yeast *Hansenula polymorpha*.

With regard to Applicant's argument that Schweden teaches away from the instant invention at column 1, lines 28-36, because the GAM1 signal sequence is taught as not leading to the secretion of gene products foreign to yeasts and that Schweden was not able to secrete the protein hirudin using the GAM1 signal sequence (Remarks, p. 14, first two paragraphs), the teaching by Schweden informs the skilled artisan that the GAM1 leader sequence alone will not support the secretion of the non-yeast protein. However, one of ordinary skill in the art would know and understand from this teaching that a yeast

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promoter sequence or a sequence with a KEX2 recognition site must be used in order to secrete the heterologous protein of interest if using the GAM1 leader sequence. As stated of record, Schweden also teaches the KEX2 processing signal recognition site from *Saccharomyces*, which consists of the dipeptide Lys-Arg that is also recognized by other yeasts (column 2, lines 32-34). Additionally, MOX and FMD promoters, which are yeast promoters that are well-known in the art, are taught in Example 4 (column 5, line 22). In further response to Applicant's arguments, Weydemann et al., (Appl Microbiol Biotechnol. 1995;44:377-385, especially abstract, p. 378, column 1, second and third paragraphs, Figure 1, and Table 1), teach a construct comprising the strongly inducible promoter element of the cloned key enzyme gene for methanol oxidase (MOX) followed by the signal sequence from CHH (crustacean hyperglycemic hormone), followed by the heterologous protein hirudin, and another construct comprising pMOX-GAM-Hir (with an added KEX2 recognition site) produced in the in the yeast *Hansenula polymorpha* (see p. 377, column 2, last paragraph, and Figure 1). Weydemann et al., provide evidence of the successful production of hirudin (a foreign protein) in *Hansenula polymorpha* using a MOX promoter and each of the CHH and GAM1-KEX2 sequences. Schweden also teaches that the CHH leader sequence (from the hyperglycemic hormone of the shore crab, *Carcinus maenas*), is "particularly suitable for the process" of producing heterologous foreign recombinant proteins in yeasts which comprises transforming the yeasts with an expression cassette (column 1, lines 37-44, and 64-67).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (Remarks, p. 14, third paragraph), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

With regard to Applicant's argument that the examiner's statements that the use of these signal sequences is proven, successful, and predictable, is not supported by Schweden (Remarks, p. 15, first paragraph), Applicant is also encouraged to review the additional supporting evidence provided by the examiner in the form of Weydemann et al., (*supra*), as discussed above.

Regarding Applicant's argument that the asserted prior art provides no working examples of the invention claimed in the instant application (Remarks, p. 15, first paragraph), the asserted prior art is not required to recite any working examples. Applicant is reminded that the instant rejection is a combinatorial rejection under 35 USC 103(a). However, Applicant is also encouraged to review the

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additional supporting evidence provided by the examiner in the form of Weydemann et al., (*supra*), as discussed above.

In regard to Applicant's arguments that Schweden does not teach the yield of hirudin obtained using the process taught in the examples therein (Remarks, p. 15, second paragraph), Applicant's argument is not relevant to the instant claims. The instant claims do not recite any limitations of protein yield, so a yield comparison of hirudin would be spurious to the examination of the instant claims, as written.

Regarding Applicant's arguments that the only leader sequence used in Schweden is from shore crab (SEQ ID NO: 1) and that there is no disclosure or enablement for the use of the leader sequence from *Schwanniomycetes occidentalis* (Remarks, p. 15, last paragraph to p. 16, first paragraph), Applicant's argument is not well founded. The GAM1 leader sequence from *Schwanniomycetes occidentalis* is old and well known in the art. Case law makes clear that the Schweden patent does not have to recite what is old and well known in the art. It is sufficient that Schweden identifies GAM1 by name and cites an internal reference (to G. Gellissen, 1991). The publicly available prior art enables GAM1, as disclosed by Schweden.

Regarding Applicant's argument that there is no disclosure of insulin in Schweden and that no protein other than hirudin is specifically disclosed in Schweden (Remarks, p. 16, first paragraph), Applicant is reminded that the instant rejection is a combinatorial rejection under 35 USC 103(a). Accordingly, Schweden need not teach each and every limitation of the instant claims. Applicant is also reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In regard to Applicant's argument that the instantly claimed process which is useful for making insulin "may not be useful for manufacturing other recombinant protein even when they belong to the same class" (Remarks, p. 16, first paragraph) is not supported by any evidence of record. Applicant is encouraged to review the additional supporting evidence provided by the examiner in the form of Weydemann et al., (*supra*), as discussed above.

Regarding Applicant's admission that one of skill in the art could envision the use of the process involving the leader sequence obtained from the shore crab as claimed in Schweden for the production of hirudin and analogs, but that the production of insulin would not be envisioned (Remarks, p. 17, second paragraph), Applicant's argument is without merit and is contradicted by Applicant's own admission on the record. First, Schweden teaches that any proteins can be expressed by heterologous genes (column 1,

lines 8-9). Second, Applicant admits that at the time of the instant invention that recombinant insulin was a well-established product in the market and that there were a number of patents specifically disclosing the process of producing insulin using recombinant technology (Remarks, p. 19, second paragraph).

Regarding Applicant's argument that "the use of such a process for the production of insulin would require undue experimentation" (Remarks, p. 17, second paragraph), is without support. Markussen teach a process for producing recombinant insulin. Even though the Markussen process does not use the CHH or GAM1 signal sequences of the instant claims, it would not require undue experimentation to use the CHH or GAM1 signal sequences in light of the teachings of Schweden, as evidenced by Weydemann et al., *supra*. Applicant has provided no evidence showing that a process of producing insulin would require undue experimentation. Even if the process of producing insulin would require some experimentation, a considerable amount of experimentation is permissible, if it is merely routine in the art, or if the specifications in question (such as those of the cited prior art) provides a reasonable amount of guidance with respect to the directed in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed (see, *Atlas Powder Co., v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409,413 (Fed. Cir. 1984). Applicant's argument is also contradicted by the admission of Applicant's representative, that at the time of the instant invention recombinant insulin was a well-established product in the market and that there were a number of patents specifically disclosing the process of producing insulin using recombinant technology (Remarks, p. 19, second paragraph).

With regard to Applicant's argument that there is no teaching or suggestion that the MF-alpha leader sequence taught by Markussen in the production of pre-pro-insulin be substituted with the leader sequence of the shore crab taught by Schweden (Remarks, p. 17, last paragraph), Applicant has previously made this argument of record (see Remarks filed 3/5/2008, p. 11, last two paragraphs) and it was not found to be persuasive. The examiner previously replied that the '487 patent (Schweden) itself provides the rationale and motivation to use a construct comprising vectors for the use of large (i.e. commercial-scale) secretory expression of recombinant proteins in *Hansenula polymorpha* yeasts using signal sequences from *Schwannomyces occidentalis* or the signal sequence of the crustacean hyperglycemic hormone from *Carcinus maenas*. Schweden teaches that the use of these signal sequences in these yeasts is known. Schweden also teaches that any generic protein may be used in the yeast expression system, "in particular proteins which are foreign to yeasts (i.e. heterologous), in the yeast *Hansenula*, which ensures efficient secretion and correct processing for a large number of proteins" (column 1, lines 36-41). Applicant is encouraged to review the additional supporting evidence provided

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by the examiner in the form of Weydemann et al., (*supra*), as discussed above. Further, Markussen teach production of the insulin pre-pro peptides with the addition of selective cleavage sites adjacent to the N-terminal of the pre-pro-insulin peptide sequences that are produced in yeasts that would enable subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatic or chemical cleavage. Thus, Markussen provides the rationale and motivation to use *Hansenula polymorpha* yeasts to produce recombinant proteins in using signal sequences from *Schwanniomyces occidentalis* or the signal sequence of the crustacean hyperglycemic hormone from *Carcinus maenas* and demonstrates that the commercially important, well known, and well characterized insulin pre-pro-peptide can have cleavage sites added to aid in recombinant protein expression without adversely affecting the functional properties of the peptide.

With regard to Applicant's argument that the instant invention has yielded unexpected results in that the use of the signal peptide sequences from either *Schwanniomyces occidentalis* or *Carcinus maenas* results in an unexpected high yield of insulin precursor (Remarks, p. 18, second paragraph), Applicant's argument is spurious because there is no limitation in any of the claims under examination related to protein yield. Accordingly, Applicant's argument is not relevant to the instant claims under examination.

Regarding Applicant's argument that Schweden does not provide a level of predictability (Remarks, p. 18, third paragraph), Applicant's argument is not entirely supported by the reference and the prior art. In support of this argument, Applicant states that the use of signal sequences from *Schwanniomyces occidentalis* or *Carcinus maenas* were known only for the production of proteins which were present in yeast (Remarks, p. 18, sixth paragraph). The examiner responded to this line of reasoning in great detail, above, in response to Applicant's argument that Schweden teaches away from the instantly claimed invention. Applicant's attention is directed to the examiner's response, set forth in detail above.

In response to Applicant's argument that Schweden makes unsupported conclusory statements that the process leads to a high yield of mature proteins (Remarks, p. 18, sixth paragraph) and that unexpected results must be established by factual evidence and that arguments or conclusory statements do not suffice (citing *In re De Blauwe*, 736 F2d 699, 705 (Fed. Cir. 1984)) (Remarks, p. 18, last paragraph to p. 19, first paragraph), again Applicant's argument is spurious and is not relevant to the instant claims. There is no limitation in any of the claims under examination related to protein yield. Accordingly, Applicant's argument is not relevant to the instant claims under examination.

In response to Applicant's argument that one of ordinary skill in the art would not predict the high yield of insulin by merely using the claimed signal sequences and process as taught by Schweden (Remarks, p. 19, second paragraph), again, Applicant's argument is spurious because there is no limitation

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in any of the claims under examination related to protein yield. Accordingly, Applicant's argument is not relevant to the instant claims under examination.

Regarding Applicant's argument that Hollenberg's general disclosure does not describe or suggest the using a DNA construct comprising the signal sequences from *Schwanniomycetes occidentalis* or *Carcinus maenas*, or alternatively, if Hollenberg does suggest the use of the DNA construct for the production of insulin, Hollenberg does not enable such a process (Remarks, p. 20, first paragraph), Applicant is reminded that the instant rejection is a combinatorial rejection under 35 USC 103(a). Accordingly, Schweden need not teach each and every limitation of the instant claims. Applicant is also reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant is referred to the Office Action of 10/5/2007, page 5, paragraph (c) wherein the examiner specifically states that the Hollenberg reference is an evidentiary reference that does nothing more than confirms that *Hansenula* and *Pichia* are methylotropic yeasts.

Regarding Applicant's argument that Weidemann does not disclose the cDNA sequence for the production of the insulin precursor nor does it disclose the cDNA sequence "which is not flanked by a cleavage site" (Remarks, p. 20, second paragraph), Applicant is again reminded that the instant rejection is a combinatorial rejection under 35 USC 103(a). Accordingly, Schweden need not teach each and every limitation of the instant claims. Applicant is also reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant is referred to the Office Action of 10/5/2007, page 5, paragraph (d) wherein the examiner specifically states that the Weidemann reference is an evidentiary reference that does nothing more than confirms that the shore crab signal taught by Schweden as SEQ ID NO: 1 is the same sequence (and is identical to) the crustacean hyperglycemic hormone, also called CHH, from *Carcinus maenas*. The examiner also notes that the Weidemann reference is internally cited by Schweden.

Regarding Applicant's arguments that it would not be obvious to one of ordinary skill in the art to combine the references (Remarks, p. 20, third paragraph), Applicant makes this statement without any evidentiary support. The examiner has provided prior art references, rationales, and pin-pointed citations in the references themselves to support a *prima facie* case of obviousness. Unsupported conclusory statements by Applicant's representative do not take the place of evidence and are not persuasive.

With regard to Applicant's argument that the prior art does not suggest the desirability of the claimed modifications over the prior art (Remarks, p. 21, first paragraph) and that the examiner engages in improper hindsight reasoning (Remarks, p. 21, second paragraph), Applicant is referred to the detailed explanation regarding the art's rationale, suggestion, and motivation to combine, set forth above. Additionally, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's arguments related to the multiple citation of patent case law references, the cases cited provide general guidance that: there must be a motivation, rationale, or desirability to combine the references; that the prior art must themselves teach or suggest the motivation to combine; that the suggestion to combine should not come from the Applicant; that a *prima facie* case must be established in the form of some teaching, suggestion, incentive, or inference in the applied prior art or in the form of generally available knowledge that one of ordinary skill in the art would have been led to combine the teachings of the prior art; and that the examiner include an explanation in the form of a factual basis to support the conclusion that it would have been obvious to make the combination. However, none of the cases are on point with the facts in the instant case and they do nothing more than recite the considerations to be undertaken when considering and setting forth a *prima facie* case in an obviousness rejection. The examiner set forth a detailed finding of facts, conclusions of law, and rationale for combining the references in the Office Action of 10/5/2007 (pp. 3-8). The examiner responded to each of Applicant's arguments in the Office Action of 6/19/2008 (pp. 2-6). The examiner has addressed Applicant's responses and argument' herein and continues to find Applicant's arguments unpersuasive.

To recap, Markussen teaches DNA constructs comprising human insulin precursors containing the peptide chain B(1-29)-A(1-21) of human insulin with a bridging chain connecting the carboxyl terminus of the B(1-29)-chain with the amino terminus of the A(1-21)-chain, by the formula B(1-29)-(X_n-Y)_m-A(1-21) [referred to as formula I], where n is an integer from 0 to 33 and m is 0 or 1 (column 2, lines 54-67 to column 3, lines 1-11) (compare instant claim 1). Formula I where m is 0 (meaning that there is no linker other than a direct peptide bond between B(1-29) and A(1-21)) is taught at column 3, lines 8-11 and claims 1 and 2 (compare instant claim 1). The DNA construct is prepared by culturing a

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yeast host transformed with a replicable expression vehicle capable of expressing a DNA-sequence encoding the insulin precursor (column 3, lines 20-23; column 4, lines 48-60) (compare instant claim 25). Expression using a yeast promoter is taught at column 4, lines 57-58. Secretion using a leader sequence is taught at column 4, lines 40-47) (compare instant claims 1 and 23). A method for preparing human insulin is taught whereby a yeast strain is transformed with a replicable expression vehicle comprising a DNA-sequence encoding the insulin precursors of the recited formula I the transformed yeast strain is cultured in a suitable nutrient medium, the insulin precursors are recovered from the culture medium and converted in vitro into human insulin (column 4, lines 63-68 to column 5, lines 1-2) (compare instant claim 25). Markussen teaches the addition of selective cleavage site adjacent to the N-terminal of the B(1-29)-chain of the insulin precursors enabling subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatic or chemical cleavage (column 3, lines 60-64) (compare instant claims 4-11). Cleavage at a methionine adjacent to the desired protein is taught at column 4, lines 25-26 (compare instant claims 8 and 9). Arginine and lysine cleavage sites adjacent to the desired protein enables cleavage with trypsin-like proteases (column 4, lines 26-28) (compare instant claims 10 and 11). When the insulin precursor is expressed in yeast the sequence may contain two basic amino acids (e.g. Lys-Arg or Arg-Lys) adjacent to N-terminal of the B(1-29)-chain of the insulin precursor, because yeast are able to cleave the peptide bond between the basic amino acids and the precursor (column 4, lines 9-14) (compare instant claims 10 and 11). [Examiner note: because instant claims 10 and 11 recite the word "has" following the preamble, the Examiner interprets "has" as "comprises." The claim is read as "comprises either a single arginine or a single lysine residue..." Because of the open-ended claim terminology, claims 10 and 11 do not exclude the use of a dipeptide arg-lys or lys-arg, so long as there is only one lys or one arg. See also MPEP 2111 and 2111.03.] Markussen does not teach the DNA construct with signal sequences from the species of *Schwanniomyces occidentalis* glucoamylase or *Carcinus maenas* crustacean hyperglycemic hormone.

Schweden teaches construction of vectors for the secretory expression of recombinant proteins from the yeast *Hansenula polymorpha* (entire document, especially Example 1, column 3; and Example 2, column 4) (compare instant claims 25, 26, and 27). The glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is taught as an applicable signal peptide (column 1, lines 28-30) (compare instant claims 1 and 2) and the leader sequence from the hyperglycemic hormone of the shore crab, which consists of residues 1-26 of SEQ ID NO: 1 (column 1, lines 64-67) (compare instant claims 1 and 3). The shore crab signal sequence taught by Schweden is identical to the signal sequence of the crustacean hyperglycemic hormone (CHH) from *Carcinus maenas* (see column 1, lines 62-64, internally citing the

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Weidemann et al., reference). Schweden also teaches the KEX2 processing signal recognition site from *Saccharomyces*, which consists of the dipeptide Lys-Arg and is also recognized by other yeasts (column 2, lines 32-34) (compare instant claims 4-7, 10, and 11). MOX and FMD promoters are taught in Example 4 (column 5, line 22) (compare instant claim 24). Yeasts of the genera *Hansenula*, *Saccharomyces*, *Kluyveromyces*, and *Pichia* are taught in claim 3 (compare instant claim 26). Yeasts of the genera *Hansenula* and *Pichia* are methylotrophic yeasts.

A person of ordinary skill in the art at the time the invention was made would have reasonably know that DNA constructs could be made in yeasts by using known promoter sequences, known signal proteins for optimal/high efficiency protein expression, and the known pre-pro peptide sequence of insulin, human or of non-human origin. Further, a person of ordinary skill in the art would have been able to make the DNA construct merely by using well-known methodologies and protocols, such as the ones taught by the Markussen and Schweden, and the resulting structure of the DNA construct and expression of insulin proteins would have been predictable.

In view of the facts recited above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention. The person of ordinary skill in the art could have combined the elements as claimed by known methods to produce a DNA construct with the instantly recited limitation. One of skill in the art would have recognized that the results of the combination of a yeast promoter, a well-known signal peptide from either of the recited species, a human or animal insulin pre-pro peptide sequences, with or without a KEX protease cleavage site, with or without a single methionine residue, a single arginine residue, or a single lysine residue at the N-terminal of the pre-pro-insulin peptide, a process of using a well-known yeast promoters MOX and FMD, by transforming yeasts, including the genera *Hansenula*, *Saccharomyces*, *Pichia*, and *Kluyveromyces*, and the species *Hansenula polymorpha* with a plasmid carrying the DNA construct, expressing the transformed yeasts in culture, and isolating the insulin containing polypeptide from the culture would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made. It would have also been obvious to use the MOX (methanol oxidase) promoter, for example, in methylotrophic yeasts, such as *Hansenula polymorpha* and *Pichia* species. It is noted that each of the KEX site, methionine precursor, arginine and lysine precursors are all equivalent alternative cleavage sites in the processing of peptides in yeasts, as taught by both the Markussen and the Schweden patents.

With regard to the arguments of Applicant's representatives on p. 22 of the Remarks, drawn to the examiner's alleged failure to specifically address the expressly recited features of the claims, contrary to MPEP 707.07(g), Applicant is specifically referred to the Office Action mailed 10/5/2007, pages 3-8, where the rejection under 35 USC 103(a) specifically recites findings of fact and conclusions of law that are supported by page and line number references as well as references to the correlating limitation in each of the instantly rejected claims. Applicant is also specifically referred to the Office Action mailed 6/19/2008, pages 3-6, which specifically responds to Applicant's arguments (filed 3/5/2008) on a point-by-point basis, providing specific pin-citations from the prior art references and applicable case law. The examiner has complied with her burden of establishing a *prima facie* case of obviousness and has at all times provided Applicant with detailed information in order to advance prosecution.

The wholly unsupported accusations of Applicant's representative (especially on p. 22 of the Remarks) do not point out, disclose, or reference any specific defect in the examiner's provision of the information necessary to resolve issues related to patentability. Instead, Applicant's representative engages in unprofessional hyperbole, making wholly unsupported accusations that the examiner has allegedly "prevented Applicant from providing appropriate patentability arguments and/or rebuttal evidence." These arguments are entirely without merit and do not serve Applicant's interest nor advance the prosecution of the case. Applicant's representative is cautioned that while he is free to disagree with the examiner on the merits of any case, unsubstantiated, pejorative attacks and accusations as to the examiner's professionalism will not be tolerated and will be referred to the Office of Enrollment and Discipline for investigation.

New Claim Rejections
Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-11 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al., US Patent 4,916,212 (10 April 1990) and Weydemann et al., (Appl Microbiol Biotechnol. 1995;44:377-385).

The Examiner finds the following facts:

- a. The claims are drawn to a DNA construct with the formula pY-SP-B(1-29)-A(1-21), wherein the promoter is a yeast promoter, wherein SP encodes a signal peptide from the recited species of *Schwanniomyces occidentalis* glucoamylase signal peptide sequence or from *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequence, B(1-29) and A(1-21) are from the coding sequences of an insulin pre-pro-peptide, linked by means of a peptide bond; wherein the construct does or does not carry a KEX protease cleavage site; wherein the construct comprises a single methionine residue at the N-terminus of the B(1-29)-A(1-21) region; wherein the SP has either a single arginine or a single lysine residue adjacent to the N-terminus of the polypeptide encoded by the B(1-29)-A(1-21) sequence; wherein the insulin pre-pro-peptide is human insulin; a process for the expression of insulin in yeast with the construct of claim 1; made by a process a yeast promoter selected from MOX-P, FMDH-P, FMD-P, or DHAS-P; wherein the yeast is selected from the genera *Hansenula*, *Saccharomyces*, *Pichia*, and *Kluveromyces*; wherein the species is *Hansenula polymorpha*.
- b. Markussen teaches DNA constructs comprising human insulin precursors containing the peptide chain B(1-29)-A(1-21) of human insulin with a bridging chain connecting the carboxyl terminus of the B(1-29)-chain with the amino terminus of the A(1-21)-chain, by the formula B(1-

29)-(X_n-Y)_m-A(1-21) [referred to as formula I], where n is an integer from 0 to 33 and m is 0 or 1 (column 2, lines 54-67 to column 3, lines 1-11) (compare instant claim 1). Formula I where m is 0 (meaning that there is no linker other than a direct peptide bond between B(1-29) and A(1-21)) is taught at column 3, lines 8-11 and claims 1 and 2 (compare instant claim 1). The DNA construct is prepared by culturing a yeast host transformed with a replicable expression vehicle capable of expressing a DNA-sequence encoding the insulin precursor (column 3, lines 20-23; column 4, lines 48-60) (compare instant claim 25). Expression using a yeast promoter is taught at column 4, lines 57-58. Secretion using a leader sequence is taught at column 4, lines 40-47) (compare instant claims 1 and 23). A method for preparing human insulin is taught whereby a yeast strain is transformed with a replicable expression vehicle comprising a DNA-sequence encoding the insulin precursors of the recited formula I the transformed yeast strain is cultured in a suitable nutrient medium, the insulin precursors are recovered from the culture medium and converted in vitro into human insulin (column 4, lines 63-68 to column 5, lines 1-2) (compare instant claim 25). Markussen teaches the addition of selective cleavage site adjacent to the N-terminal of the B(1-29)-chain of the insulin precursors enabling subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatic or chemical cleavage (column 3, lines 60-64) (compare instant claims 4-11). Cleavage at a methionine adjacent to the desired protein is taught at column 4, lines 25-26 (compare instant claims 8 and 9). Arginine and lysine cleavage sites adjacent to the desired protein enables cleavage with trypsin-like proteases (column 4, lines 26-28) (compare instant claims 10 and 11). When the insulin precursor is expressed in yeast the sequence may contain two basic amino acids (e.g. Lys-Arg or Arg-Lys) adjacent to N-terminal of the B(1-29)-chain of the insulin precursor, because yeast are able to cleave the peptide bond between the basic amino acids and the precursor (column 4, lines 9-14) (compare instant claims 10 and 11). [Examiner note: because instant claims 10 and 11 recite the word "has" following the preamble, the Examiner interprets "has" as "comprises." The claim is read as "comprises either a single arginine or a single lysine residue..." Because of the open-ended claim terminology, claims 10 and 11 do not exclude the use of a dipeptide arg-lys or lys-arg, so long as there is only one lys or one arg. See also MPEP 2111 and 2111.03.]

c. Markussen does not teach the DNA construct with signal sequences from the species of *Schwannomyces occidentalis* glucoamylase or *Carcinus maenas* crustacean hyperglycemic hormone.

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d. Weydemann et al., teach the use of the strongly inducible promoter element of the cloned key enzyme gene for methanol oxidase (MOX) and a MOX-gene-derived terminator segment, followed by the signal sequence from CHH (crustacean hyperglycemic hormone), followed by the heterologous protein hirudin, and another construct comprising pMOX-GAM-Hir (with an added KEX2 recognition site) produced in the yeast *Hansenula polymorpha* (see abstract, p. 377, column 2, last paragraph; p. 378, column 1, second and third paragraphs; Figure 1; and Table 1) (compare instant claims 1-7, 10, 11, and 24-27). Figure 1 of Weydemann also show the three constructs using pMOX-MF-alpha-Hir, pMOX-CHH-Hir, and pMOX-GAMKEX2-HIR (see also, Table 1).

e. A person of ordinary skill in the art at the time the invention was made would have reasonably know that DNA constructs could be made in yeasts by using known promoter sequences, known signal proteins for high efficiency protein expression, and the known pre-pro peptide sequence of insulin, human or of non-human origin. Further, a person of ordinary skill in the art would have been able to make the DNA construct merely by using well-known methodologies and protocols, such as the ones taught by the Markussen and Weydemann and that the resulting structure of the DNA construct would have been predictable.

f. A person of ordinary skill in the art would be motivated to substituted the MF-alpha leader sequence taught by Markussen with the CHH or GAM1 or GAMKEX2 sequences taught by Weydemann based on the multiple constructs taught by Weydemann using these multiple leader sequences (see Figure 1 and Table 1).

In view of the facts recited above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention.

Markussen teaches DNA constructs comprising human insulin precursors containing the peptide chain B(1-29)-A(1-21) of human insulin with a bridging chain connecting the carboxyl terminus of the B(1-29)-chain with the amino terminus of the A(1-21)-chain, by the formula $B(1-29)-(X_n-Y)_m-A(1-21)$ [referred to as formula I]. Markussen teaches that the DNA construct is prepared by culturing a yeast host transformed with a replicable expression vehicle capable of expressing a DNA-sequence encoding the insulin precursor. Secretion using a MF-alpha leader sequence is taught at column 4, lines 40-47. A method for preparing human insulin is taught whereby a yeast strain is transformed with a replicable expression vehicle comprising a DNA-sequence encoding the insulin precursors of the recited formula I

the transformed yeast strain is cultured in a suitable nutrient medium, the insulin precursors are recovered from the culture medium and converted *in vitro* into human insulin. Markussen also teaches the addition of selective cleavage site adjacent to the N-terminal of the B(1-29)-chain of the insulin precursors enabling subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatic or chemical cleavage (column 3, lines 60-64). Cleavage at a methionine adjacent to the desired protein is taught at column 4, lines 25-26. Arginine and lysine cleavage sites adjacent to the desired protein enables cleavage with trypsin-like proteases (column 4, lines 26-28). When the insulin precursor is expressed in yeast the sequence may contain two basic amino acids (e.g. Lys-Arg or Arg-Lys) adjacent to N-terminal of the B(1-29)-chain of the insulin precursor, because yeast are able to cleave the peptide bond between the basic amino acids and the precursor (column 4, lines 9-14). Markussen does not teach the DNA construct with signal sequences from the species of *Schwanniomyces occidentalis* glucoamylase or *Carcinus maenas* crustacean hyperglycemic hormone.

Weydemann et al., teach the use of the strongly inducible promoter element of the cloned key enzyme gene for methanol oxidase (MOX) and a MOX-gene-derived terminator segment, followed by the signal sequence from CHH (crustacean hyperglycemic hormone), followed by the heterologous protein hirudin, and another construct comprising pMOX-GAM-Hir (with an added KEX2 recognition site) produced in the in the yeast *Hansenula polymorpha* (see abstract, p. 377, column 2, last paragraph; p. 378, column 1, second and third paragraphs; Figure 1; and Table 1). Figure 1 of Weydemann also show the three constructs using pMOX-MF-alpha-Hir, pMOX-CHH-Hir, and pMOX-GAMKEX2-HIR (see also, Table 1).

A person of ordinary skill in the art would be motivated to substituted the MF-alpha leader sequence taught by Markussen with the CHH or GAM1 or GAMKEX2 sequences taught by Weydemann based on the multiple constructs taught by Weydemann using these multiple leader sequences (see Figure 1 and Table 1).

A person of ordinary skill in the art at the time the invention was made would have reasonably know that DNA constructs could be made in yeasts by using known promoter sequences, known signal proteins for high efficiency protein expression, and the known pre-pro peptide sequence of insulin, human or of non-human origin. Further, a person of ordinary skill in the art would have been able to make the DNA construct merely by using well-known methodologies and protocols, such as the ones taught by the Markussen and Weydemann and that the resulting structure of the DNA construct would have been predictable.

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The person of ordinary skill in the art could have combined the elements as claimed by known methods to produce a DNA construct with the instantly recited limitation. One of skill in the art would have recognized that the results of the combination of a yeast promoter, a well-known signal peptide from either of the recited species, a human or animal insulin pre-pro peptide sequences, with or without a KEX protease cleavage site, with or without a single methionine residue, a single arginine residue, or a single lysine residue at the N-terminal of the pre-pro-insulin peptide, a process of using a well-known yeast promoters MOX and FMD, by transforming yeasts, including the genera *Hansenula*, *Saccharomyces*, *Pichia*, and *Kluyveromyces*, and the species *Hansenula polymorpha* with a plasmid carrying the DNA construct, expressing the transformed yeasts in culture, and isolating the insulin containing polypeptide from the culture would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made in light of the teachings of Markussen and Weydemann, and particularly in light of the substitutability of the MF-alpha promoter taught by Markussen with either of the CHH or GAMKEX signal peptides taught by Weydemann. It would have also been obvious to use the MOX (methanol oxidase) promoter in methylotropic yeasts, such as *Hansenula polymorpha* and *Pichia* species. It is noted that each of the KEX site, methionine precursor, arginine and lysine precursors are all equivalent alternative cleavage sites in the processing of peptides in yeasts, as taught by both the Markussen and Weydemann. This is demonstrated by the fact that DNA constructs meeting all of the claim limitations and methods of making them are taught by Weydemann.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:30am-6:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cherie M. Woodward/
Primary Examiner, Art Unit 1647